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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/468,145	06/06/95	ENGEL J	Y17506/93-11

HM12/0405

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EXAMINER	
MINNIFIELD,N	
ART UNIT	**PAPER NUMBER**
1645	22

DATE MAILED: 04/05/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/468,145	ENGEL ET AL
Examiner	**Group Art Unit**
N. M. Minnifield	1645

☒ Responsive to communication(s) filed on *Jan 20, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *20-23, 9, 10* is/are pending in the application.

Of the above, claim(s) *9, 10* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *20-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The request filed on January 20, 1999 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/468145 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicants' amendment filed January 20, 1999 is acknowledged and has been entered. Claims 12- 19 have been canceled. Claim 23 has been amended. Claims 20-23 are now pending in the present application. All rejections have been withdrawn, in view of Applicants' amendment, with the exception of those discussed below.

3. Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Callahan et al, Finkenaur (EP 88-308573), Reissman et al and Moore, taken with Sauerbier et al. This rejection is maintained for the reasons set forth below.

Callahan et al teach "...removal of the HF under vacuum, the resin was washed with ether and air dried. The resin was then extracted with 10% HOAc (120 ml), 1% HOAc (120 ml) and water (120 ml). The aqueous extracts were combined, diluted with water and lyophilized to yield 213 mg crude linear peptide. 100 mg crude linear peptide was purified by gel filtration on G-15 with 1% HOAc to yield." (col 13, l. 8-14). The prior art teaches solubilization of heptapeptide in approximately 100-10,000 parts by weight of acetic acid for each part of peptide wherein the

peptide is subsequently transferred to water followed by lyophilization. Finkenaur et al teach a method of lyophilizing a decapeptide in the presence of the bulking agent mannitol. Reissman et al discloses the use of cetrorelix in a pharmaceutical composition. Moore et al teach the conventional method of lyophilization; the lyophilizing peptides of 3-15 amino acids after solubilization in a sufficient amount of acetic acid to form a solution (cols. 7-8). The prior art teaches the claimed invention except for specifically reciting that the product was a sterile lyophilizates.

However, Sauerbier et al teach the lyophilization of a product for use and that this peptide had been sterilized (abstract; claims). Sauerbier et al teach "...sterile filtration of the solution only occurs immediately before filling into injection jars. This ensure greater microbiological safety than does the of sterile crystallizate." (col. 2). Sauerbier et al teaches that the prepared solution is sterilized by filtration using pathogen proof filters conventionally used for this purpose..." (col. 6, l. 41-43).

The claims are directed to a method of preparing a sterile lyophilizates of gel-forming peptide salts by dissolving peptide salts in acetic acid to form a solution, diluting the solution with water, adding a bulking agent, and sterile-filtering the solution, dispensing into vials and lyophilizing the solution.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to incorporate the method of Callahan et al, the addition of the bulking agent mannitol as taught by Finkenaur with the reasonable expectation of success of making a lyophilizate of

cetrorelix as taught in Reissmann et al. The prior art teaches the concept of lyophilizing small peptides. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to sterile filter the peptide so that it would be in a sterile form for administration to a human; solubilization of peptides after dissolution in acetic acid will result in stabilization of the peptide and therefore greater usefulness in pharmaceutical applications. The claimed invention is prima facie obvious in view of the prior art absent any convincing evidence to the contrary.

Applicant's arguments filed April 20, 1998 have been fully considered but they are not persuasive. Applicants have asserted that Finkenauer would not suggest to one skilled in the art how to make a sterile lyophilisate of the decapeptide Cetrorelix; and that one can not compare a decapeptide with a polypeptide. Applicants have asserted that the prior art does not disclose a medically usable sterile lyophilized Cetrorelix or such a sterile peptide. The method as claimed can be used for any size peptide or polypeptide; it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the appropriate filter for sterile filtration of a peptide or polypeptide. It would have also been obvious to a person of ordinary skill in the art at the time the invention was made to sterile for the purpose of having a medicinal or pharmaceutical composition to be administered to a patient. Sauerbier et al discloses sterilization via filtration for safety purposes to avoid contamination (col. 2). It is noted that Applicants have argued against the references individually; however, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicant's arguments filed October 20, 1998 have been fully considered but they are not persuasive. Applicants' arguments have been previously addressed. Applicants have asserted that the person of ordinary skilled in the art would not be able to conclude from the cited art that by solubilizing a gel-forming peptide in acetic acid, a sterile filterable solution can be manufactured. Applicants have asserted that gel-forming properties of a peptide are caused by interaction between molecules. These properties depend very strongly on the chemical structure of the peptide and can't be reliably predicted. The properties also depend on concentration of solution and time allowed. However, Applicants have not shown that these are critical elements to the claimed novelty or unobviousness of the claimed invention. Applicants have not provided any evidence of unexpected results.

Applicant's arguments filed January 20, 1999 have been fully considered but they are not persuasive. It is noted that Applicants' amendment to claim 23 is still prima facie obvious in view of the prior art. Applicants assert that Callahan would not lead a person of skill in the art to the present invention. Applicants assert that a person of skill in the art would not glean any information from Finkenauer as to how to make a sterile lyophilisate of the decapeptide Cetrorelix. Applicants assert that Reismann does not describe a medially usable, sterile lyophilized Cetrorelix. Applicants assert that none of the references disclose sterile lyophilisate. It is noted that Applicants' arguments have been previously addressed. It is noted that Applicants have argued against the references individually; however, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The claimed invention is prima facie obvious in view of the prior art absent any convincing evidence to the contrary.

4. The amendment filed January 20, 1999 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: 20-10000.

Applicant is required to cancel the new matter in the reply to this Office action.

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is (703) 305-3394. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield

March 18,.1999

ANITA MINNIFIELD
PRIMARY EXAMINER